**The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn**

The Examiner has rejected claims 1-18 under §103(a) as being unpatentable over Mak et al. (US Patent 5,700,682) and in view of Vu-Dac et al. (*J. Biol.Chem.* 272(36): 22401-22404,1997). Applicants respectfully traverse this rejection for the reasons stated below.

Mak et al. discloses a method for screening retinoid X receptor agonists or antagonists using a retinoid X receptor (RXR) expressed in a yeast-based expression system. Specifically Mak teaches that RXR receptors promote the expression of apolipoprotein A-I (apo A-I) (col.6, lines 58-61). Additionally, Mak discloses that the orphan receptor,HNF4, alters the magnitude of the transactivation site A of the apolipoprotein A-I gene and that alteration in the plasma levels of apo A-I and HDL may play a role in the prevention or regression of atherosclerosis. Mak makes no reference to the role of the RXR receptor as relates to activation of the apo C-III gene or the role of the ROR receptor in activation of the apo A-I gene or the apo C-III gene.

Vu-Dac discloses the role of RORα receptors in the transcriptional regulation of the apo A-I gene. Vu-Dac identified RORα as a positive regulator of rat and mouse apo A-I gene transcription. The results of Vu-Dac demonstrated that apo A-I is a direct target for RORα1 and that its expression in the intestine is under the control of RORα1. (see page 22403, last paragraph).Vu-Dac does not disclose the role of RORα as pertains to activation or regulation of the apo C-III gene.

The instant invention involves the apo C-III gene ( see e.g., specification at page 3, lines 11-14). Moreover, Applicants have discovered that the human apo A-I gene is insensitive to ROR which presumably can be attributed to sequence deviations in the respective promoter regions of the genes (specification at p. 3, lines 3-10 and figure 13). Thus, Applicants' invention is not suggested by Mak and Vu-Dac. Mak and Vu-Dac, in combination, would actually teach away from the instant invention. Both Mak and Vu-Dac are directed to the role of either ROR or RXR receptors in the transcriptional activation of the apo A-I gene, with no discussion of the apo C-III gene. Thus, the combination of references does not yield Applicants' invention, especially in view of the fact that the results obtained in mice are not extrapolatable to humans as the human gene for apo A-I is insensitive to RORα.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the

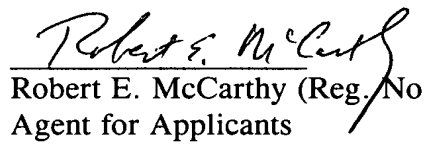
combination. *In re Geiger* (CAFC 1987) 815 F.2d 686, 2 PQ2d 1276. In the instant case, the two prior art references would actually teach away from Applicants' invention.

Therefore, Applicants' invention is not obvious in view of Mak and Vu-Dac and any rejection based on obviousness should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned **"Version with Markings to Show Changes Made"**.

In view of the above remarks and amendments, it is submitted that this application is ready for allowance. Early notice to this effect is solicited.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS**

1. (Amended) A method of screening a substance for usefulness in the treatment of lipid metabolism dysfunction comprising contacting said substance with a ~~Use of the~~ ROR ~~receptors~~ receptor, ~~and/or their~~ a response element thereof or ~~alternatively of~~ a functional equivalent ~~thereof for the screening of substances having antiatherosclerotic properties~~ of said receptor or response element, involved in the regulation of the apo C-III gene, and measuring the level of apo C-III gene expression.

2. (Amended) ~~Use~~ The method according to claim1, ~~characterized in that~~ wherein the ROR receptor and the response element of the ROR receptor are the RORα receptor or the response element of the RORα receptor.

3. (Amended) A method of screening a ~~substances~~ substance for ~~useful~~ usefulness in the treatment of a lipid metabolism ~~dysfunctions~~ dysfunction ~~characterized in that the test~~ comprising contacting said substance ~~is brought into contact~~ with (a) a receptor of the ROR family involved in the regulation of the expression of the apo C-III gene, ~~or~~ (b) a response element of the ROR receptor ~~and/or~~ (c) a nuclear factor capable of functionally coupling ROR to the RNA polymerase complex, or (d) a functional equivalent ~~thereof~~ of (a)-(c) and then measuring ~~by any appropriate means~~:

i) the binding of ~~the~~ said substance to the ROR receptor ~~and/or~~ or its functional equivalent or the binding of the complex formed ~~of the~~ by said substance and the ROR receptor to its response element and/or or to a nuclear factor capable of functionally coupling ROR to the RNA complex, ~~and/or~~ or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising ~~the~~ said response element.

4. (Amended) The method of screening according to claim 3, ~~characterized in that it comprises the following steps~~ comprising:

a) transfecting a cellular host ~~is transfected~~ with a DNA fragment

encoding an ROR receptor or one of its functional equivalents,

b) cotransfecting the host in ~~step~~ (a) ~~is cotransfected~~ with a construct comprising a response element of ~~the~~ said ROR receptor and at least one reporter gene,

c) measuring the expression of the reporter gene in the presence of the test substance ~~is measured by any appropriate means~~.

5. (Amended) The method of screening according to claim 3, ~~characterized in that it comprises the following steps~~ comprising:

a) creating a plasmid ~~is created~~ which comprises several copies of a response element recognized by ROR cloned upstream of a strong heterologous promoter placed so as to control which controls the expression of a reporter gene,

b) transfecting the construct of ~~step~~ a) ~~is transfected~~ into host cells which express ROR naturally or artificially,

c) incubating the host cells of ~~step~~ (b) ~~is incubated~~ in the presence of the test substance; and

d) measuring the activity of the reporter gene ~~is measured by any appropriate means~~.

6. (Amended) The method of screening according to claim 3, ~~characerterized in that it comprises the following steps~~ comprising:

a) creating a plasmid ~~is created~~ which comprises several copies of a response element recognized by ROR cloned upstream of a promoter which controls the expression of a selectable gene.,

b) transfecting the construct of ~~step~~ a) ~~is transfected~~ into a cellular host;

c) cotransfecting the host of ~~step~~ b) ~~is cotransfected~~ with the aid of a vector expressing ROR;

d) incubating the host of ~~step~~ c) ~~is incubated~~ in the presence of the test substance; and

e) measuring the cellular survival of said cellular host in the presence

of ~~the~~ a toxic prodrug ~~is measured by any appropriate means~~.

7. (Amended) The method of screening according to claim 3, ~~characterized in that it comprises the following steps~~ comprising:

a) ~~creating~~ a plasmid ~~is created~~ which comprises several copies of a response element recognized by the yeast nuclear factor Gal4 cloned upstream of a strong promoter which the controls the activity of ~~the~~ a reporter gene,

b) creating ~~the~~ a plasmid ~~is created~~ from a chimera which comprises the DNA binding domain of Gal4 and the DEF domains or ROR which are the ROR domains to which the ligands bind,

c) cotransfecting the plasmids ~~obtained~~ in ~~steps~~ (a) and (b) ~~are cotransfected~~ into a cellular host,

d) incubating the host of ~~step~~ (c) ~~is incubated~~ in the presence of the a test substance; and

e) measuring the activity of ~~the~~ said reporter gene ~~is measured by any appropriate means~~.

8. (Amended) The method of screening according to claim 3, ~~characterized in that it compromises the following steps~~ comprising:

a) transforming ~~a~~ the cellular host ~~as defined above is transformed~~ with a construct carrying a gene encoding the ROR receptor or its functional equivalent ~~and/or~~ or a response element of the ROR receptor, ~~then~~ and;

b) assaying ~~the~~ said cellular ~~hosts~~ host or an ~~extracts~~ extract thereof for the ~~are used in "binding" tests based on~~ competitive displacement ~~between a cold ligand and a labelled ligand~~ in the binding of a labelled and unlabelled ligand to said ROR receptor.

9. (Amended) The method of screening according to either of ~~claims~~ claim 4 ~~and 8~~, ~~characterized in that~~ wherein the construct carrying a gene encoding the ROR receptor or a response element of the ROR receptor also comprises a reporter gene.

10. (Amended) The method of screening according to claim 9, ~~characterized in that~~ wherein the reporter gene is chosen from the gene for chloramphenicol acetyltransferase, the gene for the luciferase from firefly or from Renilla, the gene for beta-galactosidase or the gene for apo C-III.

11. (Amended) The method of screening according to claim 4 ~~characterized in that~~ wherein the cellular host is chosen from mammalian cells, bacteria, ~~or~~ yeasts, or ~~alternatively~~ insect cells.

12. (Amended) The method of screening according to claim 3, ~~characterized in that, in addition~~, wherein the effect of ~~the~~ said substance on the expression of apo C-III ~~is determined by any appropriate means~~.

13. (Amended) The method of screening according to claim 3, ~~characterized in that~~ wherein the ROR receptor and the response element of the ROR receptor are the RORα receptor ~~or~~ and the response element of the RORα receptor.

14. (Amended) A method of preparing ~~Use of a substance selected by a method of screening according to claim 3 for the preparation of~~ a pharmaceutical composition or a medicament useful in ~~for the treatment and/or prevention of~~ treating or preventing atherosclerosis in human or animals comprising or selecting a substance screened according to claim 3.

15. (Amended) A method for treating or preventing atherosclerosis in humans or animals comprising modulating the expression of apo C-III gene using a medicament or a pharmaceutical composition ~~useful for the treatment and/or prevention of atherosclerosis in humans or animals~~ comprising a substance selected according to claim 3.

16. (Amended) A method for treating or preventing atherosclerosis in humans or animals comprising administering a medicament or a pharmaceutical composition comprising

a substance capable of binding to the ~~Use of a substance capable of binding to~~ the ROR receptor, or its response element ~~for the prpearation of a pharmaceutical composition useful for the treatment and/or prevention of atherosclerosis in humans or animals~~ or a functional equivalent thereof involved in the regulation of the apo C-III gene.

17. (Amended) The method according to ~~Use of a method of screening~~ claim 3, ~~for the characterization, justification and claiming of the mechanism of action of substances having antiatherosclerotic properties using the ROR receptors and/or their response elements as well as their effect on apo C-III wherein the substance has antiatherosclerotic properties~~ wherein the substance has antiatherosclerotic properties.

18. (Amended) A method of screening according to claim 8, ~~characterized in that~~ wherein the construct carrying a gene encoding the ROR receptor or a response element of the ROR receptor also comprises a reporter gene.

**Claims 19-22 have been newly added and, therefore, no marked-up version is necessary.**